IMPORTANT MEDICINE SAFETY INFORMATION

17 September 2025

VALPROATE-CONTAINING MEDICINES: POTENTIAL RISK OF NEURODEVELOPMENTAL DISORDERS IN OFFSPRING OF FATHERS TREATED WITH VALPROATE IN THE THREE MONTHS PRIOR TO CONCEPTION

Dear Healthcare Professional

In collaboration with the South African Health Products Regulatory Authority (SAHPRA), the pharmaceutical companies listed below would like to inform you about the potential risk of neurodevelopmental-disorders (NDDs) in children (from 0 to 11 years old) of men treated with valproate, as monotherapy in the three (3) months prior to conception compared to those born to men treated with two other anti-seizure medicines, lamotrigine or levetiracetam as monotherapy.

Summary

- There is a potential risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception.
- Treatment with valproate in male patients should be regularly reviewed by prescribers to evaluate whether valproate remains the most suitable treatment, particularly, when the patient is planning to conceive a child.
- Male patients should be advised to not donate sperm during treatment and for at least 3 months after treatment discontinuation.
- A patient guide should be provided to male patients and female sexual partners (of child-bearing age) to men on valproate-containing medicines, while using valproate and for 3 months after stopping the treatment.

Background on the safety concern

Valproate-containing medicines are available in powder for injection/infusion solution, tablet/capsule and liquid formulations indicated for:

- Generalised epilepsy, particularly with the following patterns of seizures, absence, myoclonic, tonic-clonic, atonic and mixed.
- Partial epilepsy in simple or complex seizures, secondary generalised
    - seizures and specific syndromes (West, Lennox-Gastaut).

- Acute and maintenance treatment of manic episodes associated with bipolar disorders in adults[1].
- Prophylaxis of migraine headaches if other drugs have not shown the desired effect[1].

The potential risk of neurodevelopmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, was observed. A retrospective observational study was conducted by pharmaceutical companies of valproate-containing medicines using data from multiple registry databases in Europe, to investigate the risk of NDDs in offspring paternally exposed (in the 3 months period prior to conception) to valproate as monotherapy, compared to lamotrigine or levetiracetam as monotherapy treatment. The primary outcome of interest was NDDs (composite endpoint including autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders, movement disorders) in offspring up to 11 years of age.

- The meta-analysis of data resulted in a pooled adjusted hazard ratio (HR) of 1.50 (95% confidence intervals (CI): 1.09-2.07) for NDDs in children from fathers treated with valproate monotherapy in the 3 months prior to conception compared to the composite lamotrigine/levetiracetam monotherapy group.
- The adjusted cumulative risks of NDDs ranged between 4.0% to 5.6% in the valproate group monotherapy versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy group.

The Professional Information (PIs) and Patient Information Leaflets (PILs) of valproate- containing products listed below are being updated to inform healthcare professionals and patients about the potential risk of NDDs in children of men treated with valproate and to provide guidance regarding use of valproate in men. In addition, educational materials will be made available to healthcare professionals and male patients. These will include:

- An updated guide for healthcare professionals with a dedicated section on the use of valproate in male patients.
- A new patient guide for males, which should be provided to male patients using valproate
- An update of the existing patient card with the information for male patients to be provided by the pharmacy to the patient each time the medicine is dispensed.

[1] Not all products are approved for these indications. Please refer to the relevant market authorisation holder approved professional information for further information

Advice for Patients

- Male patients and female sexual partners to men receiving valproate-containing medicines should be warned about the potential risks of NDDs (including autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders, movement disorders) in offspring (from 0 to 11 years old) of male patients treated with valproate-containing medicines from the three months prior to conception and during pregnancy.

- Male patients and female sexual partners (of child-bearing age) to male patients receiving valproate-containing medicines should be advised to use highly effective contraception, during and three months after cessation of treatment.

- Male patients and female sexual partners to men treated with valproate-containing medicines who are planning to conceive within the next year, should be advised to seek guidance from their specialists about their treatment options.

Advice for Healthcare Professionals

- Treatment with valproate-containing medicines in male patients with child-bearing potential should be initiated and supervised by a specialist experienced in treatment of epilepsy or bipolar disorder.

- Healthcare professionals are advised not to prescribe valproate-containing medicines in male patients of child-bearing potential if there are other effective or tolerated treatment available. Individual circumstances should be evaluated for each patient, therefore in the absence of an effective and tolerated treatment, prescribers are recommended to perform and document individual benefit-risk assessment for each patient.

- Pregnancy testing should be performed on female sexual partners (of child-bearing age) of male patients before initiation of valproate-containing medicines.

- Healthcare professionals should counsel patients on valproate-containing medicines, not to stop treatment or alter their dose without a discussion with their specialist. Emphasis should be made to patients that their condition may deteriorate if treatment is stopped or altered without a consultation with their specialist.

- Suitable alternative treatment options in consultation with a specialist experienced in the management of epilepsy or bipolar disorders should be considered and discussed with male patients planning to conceive.

- Healthcare professionals are urged to report any adverse drug reactions (ADRs) or product quality problems associated with the use of the products listed below to the relevant holder of certificate of registration and to SAHPRA by completing the ADR reporting form accessible at https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/ and emailing it to adr@sahpra.org.za.

- Alternatively, healthcare professionals may report via the following eReporting link https://primaryreporting.who-umc.org/ZA.

- Additionally, reporting can be done via the Med Safety App. The App can be downloaded into a smart mobile phone through Google Play or App store. For more information on Med Safety App, please use the following link https://medsafety.sahpra.org.za/.

- For more information on ADR reporting of products listed below, please contact the SAHPRA Pharmacovigilance unit at pvqueries@sahpra.org.za or alternatively use the contact details indicated below:

HOLDER OF CERTIFICATE OF REGISTRATION	PRODUCT	ACTIVE INGREDIENT	REGISTRATION NUMBER	CONTACT DETAILS
Abex Pharmaceutica (Pty) Ltd	Velpalex 400 mg IV	Sodium valproate	53/2.5/0665	Tel: 012 997 6974 Email: vigilance@abexpharm.com
	Navalzyd 400 mg IV	Sodium valproate	53/2.5/0671.665	
Macleods Pharmaceuticals SA (Pty) Ltd	Evalex 400 mg IV	Sodium valproate	53/2.5/0668.665	Email: safety@macleodspharma.com Tel: +27 11 682 1169
ACINO PHARMA (PTY) LTD (SOUTH AFRICA)	CONVULEX 150 MG	VALPROATE	R/2.5/218	DRUGSAFETY_ZA@ACINO.SWISS
	CONVULEX 300 MG	VALPROATE	R/2.5/219	
	CONVULEX 500	VALPROATE	R/2.5/220	
	CONVULEX® SYRUP	VALPROATE 50 MG / 5ML SYRUP	W/2.5/390	
Adcock Ingram Limited	Valeptic CR 300	Sodium Valproate	44/2.5/0067	Tel: +27 11 635 0134 Adcock. Aereports@adcock.com
	Valeptic CR 500	Sodium Valproate	44/2.5/0068	
Pharmacare Ltd t/a Aspen Pharmacare	EPROLEP CR 200	SODIUM VALPROATE + VALPROIC ACID	45/2.5/0412	drugsafety@aspenpharma.com
	EPROLEP CR 300	SODIUM VALPROATE + VALPROIC ACID	45/2.5/0093	
	EPROLEP CR 500	SODIUM VALPROATE + VALPROIC ACID	45/2.5/0094	
	NAVALPRO CR 200	SODIUM VALPROATE + VALPROIC ACID	45/2.5/0411	
	NAVALPRO CR 300	SODIUM VALPROATE + VALPROIC ACID	45/2.5/0091	
	NAVALPRO CR 500	SODIUM VALPROATE + VALPROIC ACID	45/2.5/0092	
	NAVALPRO LIQUID	SODIUM VALPROATE	46/2.5/0796	
	NAVALPRO 400MG/4ML	SODIUM VALPROATE	A40/2.5/0342	
Juno Pharma SA (Pty) Ltd	NAVILIZE 100 mg/ml (3 ml)	SODIUM VALPROATE	55/2.5/0551	RP@Junopharmsa.co.za
	NAVILIZE 100 mg/ml (4 ml)	SODIUM VALPROATE	55/2.5/0552	
	NAVILIZE	SODIUM VALPROATE	55/2.5/0553	

	100 mg/ml (10 ml)			
Oethmaan Biosims (Pty) Ltd	EPIROL	SODIUM VALPROATE	S/2.5.72	pv@oethmaan.co.za
Ruby Pharmaceuticals (Pty) Ltd.	RUBILIM CR 200	SODIUM VALPROATE + VALPROIC ACID	55/2.5/0538	adr@rubypharma.co.za
	RUBILIM CR 300	SODIUM VALPROATE + VALPROIC ACID	55/2.5/0539	
	RUBILIM CR 500	SODIUM VALPROATE + VALPROIC ACID	55/2.5/0540	
SANDOZ SA (PTY) LTD	WATER FOR INJECTION LIAM 5 ML VALPROATE SODIUM LYVI 400 MG	CEREPIV IV SOLVENT and CEREPIV IV	50/2.5/1048 50/2.5/2000	Patient.safety.sac@sandoz.com avina.ramjattan@sandoz.com sandoz.dra@sandoz.com Mobile:+27 84 603 3071
sanofi-aventis south africa (pty) ltd	EPILIM CR 200	SODIUM VALPROATE + VALPROIC ACID	27/2.5/0322	ZA.drugsafety@sanofi.com Tel: +27 (0)11 256 3700
	EPILIM CR 300	SODIUM VALPROATE + VALPROIC ACID	Y/2.5/286	
	EPILIM CR 500	SODIUM VALPROATE + VALPROIC ACID	27/2.5/0323	
	EPILIM 100 CRUSHABLE	SODIUM VALPROATE	27/2.5/0500	
	EPILIM LIQUID SUGAR-FREE	SODIUM VALPROATE	J/2.5/148	
	EPILIM INTRAVENOUS	SODIUM VALPROATE	Y/2.5/43	
	EPILIZINE CR 200	SODIUM VALPROATE + VALPROIC ACID	A39/2.5/0038	
	EPILIZINE CR 300	SODIUM VALPROATE + VALPROIC ACID	A39/2.5/0039	
	EPILIZINE CR 500	SODIUM VALPROATE + VALPROIC ACID	A39/2.5/0040	
	EPILIZINE INTRAVENOUS 400	SODIUM VALPROATE	A40/2.5/0699	

Yours sincerely

Azraa PARAK Country Safety Head South Africa *sanofi-aventis south africa (pty) ltd* Signature Azraa Parak Electronically signed by: Azraa Parak Reason: Approval Date: Sep 23, 2025 16:37:45 GMT+2	**Eugene LOUW** Head of Quality Assurance and Responsible Pharmacist, Africa *Acino Pharma (Pty) Ltd* Signature Eugene Louw Electronically signed by: Eugene Louw Reason: Reviewed and Approved Date: Sep 23, 2025 16:48:12 GMT+2	**Arshad GHOOR** Responsible Pharmacist *Ruby Pharmaceuticals (Pty) Ltd* Signature A. Ghoor Electronically signed by: A. Ghoor Reason: DHCP letter approval Date: Sep 23, 2025 17:05:00 GMT+2
Deon POOVAN Responsible Pharmacist *Adcock Ingram Limited* Signature Deon Poovan Electronically signed by: Deon Poovan Reason: DHCP Letter Approval Date: Sep 25, 2025 08:06:14 GMT+2	**Shahaboodeen CHARFARAY** RA Manager *Oethmaan Biosims (Pty) Ltd* Signature: Electronically signed by: Shahaboodeen Charfaray Reason: For approval Date: Sep 25, 2025 11:28:25 GMT+2	**Lindie MARX** Responsible Pharmacist *Abex Pharmaceutica (Pty) Ltd* Signature Electronically signed by: Lindie Marx Reason: DHCP approval letter Date: Sep 25, 2025 09:13:06 GMT+2
Bhavik HIRA Responsible Pharmacist *Juno Pharma SA (Pty) Ltd* Signature BGHira Electronically signed by: BGHira Reason: DHCPL Approval Date: Sep 25, 2025 08:59:14 GMT+2	**Nikola WHELAN** Head of SA Regulatory and Responsible Pharmacist *Aspen Pharmacare* Signature Electronically signed by: Nikola Whelan Reason: Approved as Responsible Pharmacist Date: Sep 23, 2025 16:57:15 GMT+2	**Avina RAMJATTAN** Regulatory Affairs & Launch Associate Director & Responsible Pharmacist *Sandoz SA (Pty) Ltd* Signature Signed by: Avina Ramjattan 7CC59728E84D4C3...
Vanita RAJOOL Responsible Pharmacist *Macleods Pharmaceuticals SA (Pty) Ltd.* Signature		